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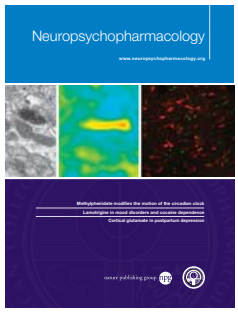

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Dopamine receptor-specific contributions to the computation of value

Short title:

Dopamine and risk taking

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Abstract

Dopamine is thought to play a crucial role in value-based decision making. However, the specific contributions of different dopamine receptor subtypes to the computation of subjective value remain unknown. Here we demonstrate how the balance between D1 and D2 dopamine receptor subtypes shapes subjective value computation during risky decision-making. We administered the D2 receptor antagonist amisulpride or placebo before participants made choices between risky options. Compared to placebo, D2 receptor blockade resulted in more frequent choice of higher risk and higher expected value options. Using a novel model fitting procedure, we concurrently estimated the three parameters that define individual risk attitude according to an influential theoretical account of risky decision making. This analysis revealed that the observed reduction in risk aversion under amisulpride was driven by increased sensitivity to reward magnitude and decreased distortion of outcome probability, resulting in more linear value coding. Our data suggest that different components that govern individual risk attitude are under dopaminergic control, such that D2 receptor blockade facilitates risk taking and expected value processing.

Introduction

Risk is common in our lives and affects many everyday decisions (for example, whether to gamble in the casino, which insurance policy to purchase, or which school to enroll in). When making decisions between risky options, people need to balance the magnitudes of potential gains and losses with the probabilities that they will occur. One possibility is to multiply the magnitudes of risky outcomes by their respective probabilities to calculate each choice option's expected value and choose the option with higher expected value irrespective of risk (Pascal, 1948). However, behavioral evidence indicates that people have individually different risk attitudes, and therefore value risky options differently. This often results in options with lower expected value being chosen if the alternative option has higher risk (Christopoulos *et al* 2009), a phenomenon known as risk aversion.

A highly influential psychological model to describe this behavior, prospect theory (Kahneman & Tversky, 1979), postulates that risk-sensitive economic choice can be described by non-linear conversion of objective outcome magnitudes and probabilities into subjective value, or utility. Specifically, prospect theory postulates that preferences over risky options can be explained by 3 parameters that define a person's utility function. Firstly, the curvature of the utility function, σ, captures whether an individual is risk averse (concave utility function) or risk seeking (convex utility function). A second parameter, α, governs how much probabilities are distorted, with smaller probabilities typically being overweighted and larger probabilities underweighted. Thirdly, a parameter (λ) that controls how much steeper the utility function is for losses than for gains captures the degree of loss aversion. Together, these parameters describe utility functions that model subjective risk attitudes by governing how individuals respond to the magnitudes and

probabilities of outcomes encountered in risky options. Prospect theory was introduced because it can explain behaviors that more traditional models such as expected utility theory (Bernoulli, 1954, von Neumann & Morgenstern, 2007) cannot explain. According to expected utility, risk preferences are driven by the curvature of the utility function, without probability distortion or loss aversion.

The neural basis for value encoding under risk has been widely investigated, with the dopaminergic system emerging as a neural substrate for processing economic value. Dopamine neurons encode reward magnitude (Schultz, 1998), combine reward magnitude with probability (Tobler *et al* 2005) into prospect theory- or expected utility-like value signal of gains in both risky and safe options (Stauffer *et al* 2014). In addition, people suffering from disease- or drug-induced modifications to the dopaminergic system demonstrate differences in risky decision making (Rogers *et al* 1999; Bornovalova *et al* 2005; Leland & Paulus, 2005). Rodent studies have shown that reward value (Howe *et al* 2013) and the subjective value of risk (Sugam *et al* 2012) is expressed in dopamine release, that risky decision making can be modulated by stimulating the inputs to dopamine neurons (Stopper and Floresco, 2014), dopamine neurons themselves (Stopper *et al* 2014), or striatal D2-receptor neurons (Zalocusky *et al* 2016) and that receptor-specific dopaminergic drugs can bias preferences for risky versus safe outcomes (Stopper *et al* 2013). However, the question of precisely how the dopaminergic system processes the components of subjective risk attitude and how the different parameters governing it are mediated by different dopamine receptor subtypes remains unanswered.

One recent model has proposed that risk attitude is governed by the balance of D1- and D2-receptor mediated activity in the dopaminergic system (Clark & Dagher, 2014; Mikhael & Bogacz, 2016). The model is compatible with animal literature (Kravitz *et al* 2012; Lee *et al*

2016; Surmeier *et al* 2014; Tai *et al* 2012) but remained largely untested. Specifically, it proposes that the subjective sensitivity to potential rewards in risky options (i.e., utility curvature) is D1-mediated, and the subjective sensitivity to potential punishments (i.e. loss aversion) is D2-mediated. Without pharmacological intervention, this sensitivity is typically reduced for larger rewards, reflected in concave utility functions from which risk aversion partly arises. By extension, a reduction in D2 mediated (inhibitory) activity should enhance sensitivity to large monetary rewards in risky options, resulting in more linear (or possibly convex) utility functions and reduced risk aversion.

To test this idea, we pharmacologically blocked D2-receptors while participants made choices between risky options. We hypothesized that D2 antagonism would decrease risk aversion by increasing the sensitivity to larger reward magnitudes and thereby reducing the concavity of the utility function (Fig. 1A). In addition, risk aversion could also be modulated through a reduction in probability distortion, allowing people to more accurately compute the probabilities associated with risky outcomes, or through a decrease in loss aversion (Fig. 1B), making people less sensitive to potential negative outcomes from risky options. Any of these effects would predict that an expected utility model would fit the data better than a prospect theory model under D2 antagonism. To test these different possibilities, we conducted a randomized double-blind, placebo-controlled pharmacological intervention in two groups of healthy participants while they performed a dynamic risky decision making task (Fig. 1C) designed to elicit their underlying risk preferences.

Methods & Materials

Participants

Using a randomized double-blind placebo-controlled between-subjects design, we recruited 93 participants from the student population at the University of Zurich and randomly assigned them to one of two groups. Both groups were matched in terms of baseline measures that may influence drug effects on the dopaminergic system, including age, sex, BMI, working memory capacity (digit span task), and mood, alertness and calmness, which were measured using the multidimensional mood state (MDMQ) questionnaire (Steyer *et al* 1997). One group received placebo (n=48) while the other received a 400mg dose of amisulpride (n=45). The results reported here form part of a larger study. In addition to the risky decision task, participants performed temporal and effort discounting tasks, a prosocial decision making task (Soutschek *et al* in press), a reversal learning task, and a stop-signal-reaction time task.

Pharmacological Manipulation

Amisulpride is a dopamine antagonist that selectively blocks neurotransmission at dopamine D2/D3 receptors (Rosenzweig *et al* 2002). At low doses (50-300mg), amisulpride primarily prevents dopamine action at presynaptic D2/D3 autoreceptors (Racagni *et al* 2004), thus effectively stimulating dopaminergic neurotransmission. At higher doses (≥400mg), amisulpride preferentially antagonizes post-synaptic D2/D3 receptors (Schoemaker *et al* 1997). The used

dose of 400 mg is thus at the lower end of postsynaptically active high doses (Müller *et al* 2002; Rosenzweig *et al* 2002) and occupies about 70% of D2 receptors (Meisenzahl *et al* 2008). To limit extrapyramidal side effects, we refrained from using higher doses. Two plasma concentration peaks are typically observed during the absorption period, with the first, lower peak occurring approximately 1-2 hours after ingestion (Le Bricon *et al* 1996).

Task

After receiving placebo or amisulpride, participants waited for 1.5 hours in the controlled laboratory environment. Participants then performed a risky decision making task (Fig. 1C), which consisted of 20 trials where they made choices between two risky options presented at the same time on the screen. The task was programmed using the Cogent toolbox (v1.32) and MATLAB (R2016b). All decisions were between 2 compound lotteries of the form p chance of magnitude x, 1-p chance of magnitude y. Lotteries were constructed on a trial-by-trial basis by combining different levels of $\{x, p, y\}$, where $p \in \{0.1, 0.3, 0.5, 0.7, 0.9\}$, $x \in \{1, 30, 40, 100, 1000\}$ and $y \in \{-20, -15, -10, -5, 5, 10, 30\}$, with x and y denominated in Swiss francs (CHF). On every trial, one lottery was presented on the left side of the screen and one on the right side, with the magnitudes and their associated probabilities on the same horizontal plane. For example, Fig. 1C illustrates a choice between a lottery on the left side that results in a gain of 100 Swiss francs with 50% chance or a loss of -15 Swiss francs with 50% chance and a lottery on the right side that results in a gain of 40 Swiss francs with 90% chance or 10 Swiss francs with 10% chance. To ensure incentive compatibility, one trial was randomly selected at the end of the experiment and the lottery chosen by the participant in that trial was realized. The outcome was added to or subtracted from the fee participants received for taking part (120 Swiss francs) in the pharmacological experiment. Specifically, participants were

instructed to treat every decision as if it were the one being selected at the end and therefore make their choices according to their true preferences. Average payout was 22.3 Swiss francs; 28 participants incurred losses.

Dynamic Task Design

After each choice, the task adaptively presented a new pair of lotteries to the participant that optimized the sequence of possible trials to recover the participant's true risk preferences. In such a way, each new lottery pair maximizes the amount of information about the participant's risk attitude, given their decisions on preceding trials. We implemented the adaptive Bayesian method described by Toubia and colleagues (Toubia *et al* 2013), where the posterior distribution over prospect theory parameters is updated after each choice and the task selects a new pair of lotteries that maximizes the amount of information over the parameters to home in on the participant's true risk attitude (Supplementary Material - Dynamic Task Design). This Bayesian approach to adaptive elicitation of risk attitude differs from the typical bisection approaches used in psychophysics (Cornsweet, 1962) and allows accurate elicitation of risk preferences within 20 trials (Supplementary Fig. S1) by adapting both the probabilities and magnitudes for both options on every trial (as opposed to keeping one option fixed as in more traditional staircase/bisection approaches).

Simulations

Simulations confirmed that the method could recover true parameter values within 20 trials (Supplementary Fig. S1) and was robust to different priors (Supplementary Fig. S2). Simulations were also conducted to assess the unique impact of each parameter on choices (Supplementary Fig. S3). Full details of these simulations can be found in the supplementary material.

Data analysis

Choice frequency data and response times were analyzed using the statistics toolbox of MATLAB in a series of t-tests and ANOVAs. The specific behavioral measures used in our model-free analysis were the proportions with which (i) the higher variance or (ii) the higher expected value lottery was chosen. Mixed-effects multiple and logistic regressions were carried out in R. For the expected value sensitivity analysis (Fig. 2D), we computed the expected values of both options for each trial, binning these values around 10, 20, 50, 70, 100, 500 and 1000CHF and created dummy variables to encode the presence of each expected value in the high risk (+1) or low risk (-1) options on each trial, and regressed participants' choices for the high risk option against these dummy variables using a mixed effects logistic regression that included both fixed and random effects for each participant. Regression parameters for each dummy variable (i.e. the influence of each expected value on risky choices) were normalized between 0 and 1, directly compared using ANOVA and plotted in Fig. 2D.

Choice Models & Fitting

Prospect theory model fitting (Figs. 2 & 3) was applied in MATLAB according to the hierarchical Bayesian framework described in detail in Toubia and colleagues (2013) using the standard cumulative prospect theory model used in the literature (Tversky & Kahneman, 1992) with standard probability weighting (Prelec, 1998) to the placebo and amisulpride groups separately. Our use of group-wise hierarchical Bayes was motivated by two factors: 1) The relatively large number of participants in each group and 2) relatively small number of trials per participant. Options are defined by $\{x, p; y\}$ with outcome x occurring with probability p and outcome y occurring with probability 1- p. Formally, the value of an option to a participant is given by:

$$U(x,p,y,\alpha,\sigma,\lambda) = \begin{cases} v(y,\sigma) + \pi(p,\alpha)\big(v(x,\sigma) - v(y,\sigma)\big) & if\ x > y > 0\ or\ x < y < 0 \\ \pi(p,\alpha)v(x,\sigma) + \pi(1-p,\alpha)v(y,\sigma) & if\ x < 0 < y \end{cases}$$

where $v(x,\sigma) = \begin{cases} x^{\sigma} & for\ x > 0 \\ -\lambda(-x^{\sigma} & for\ x < 0 \end{cases}$

and $\pi(p,\alpha) = \exp[-(-\ln p)^{\alpha}]$

In the hierarchical Bayesian framework, a uniform prior distribution of the model parameters is specified and a posterior distribution is calculated by obtaining the prior with the choice data from the participants. The hierarchical Bayesian approach also allows more accurate group estimates by simultaneously leveraging individual and group level estimates (utility curvature, σ; probability distortion, α; and loss aversion, λ), such that individual estimates deemed to be unlikely, i.e. outliers given the group distribution, receive less weight than more reliable measures. The uniform prior ensures that the mode of the posterior distribution (maximum a posteriori) is equivalent to the maximum likelihood estimate (Toubia *et al* 2013; p.620).

We assessed the fit of each model for each participant based on the softmax choice rule (supplementary methods). Expected utility and expected value models were fitted using maximum likelihood estimation. Formally, the expected utility of an option is given by:

$U(x,p,y,\sigma) = \pi(p)v(x,\sigma) + \pi(1-p)v(y,\sigma)$

where $v(x,\sigma) = x^{\sigma}$

and the expected value of an option is given by:

$U(x,p,y) = \pi(p)(x) + \pi(1-p)(y)$.

Results

In line with the observation that humans typically are risk averse (e.g., Christopoulos *et al* 2009), analysis of the choice data revealed that the placebo group was risk averse, with the proportion (45.2%) of choices of the riskier option being significantly smaller than 50% (one-sample t-test, t_{47}=-2.78, p=0.008), even though the expected value of the safer options was smaller than that of the riskier options. Importantly, compared to the placebo group, participants under dopamine D2/D3 receptor blockade were significantly less risk averse, showing more choices of the higher risk option (mixed effects logistic regression with risky choice as dependent variable, treatment as primary independent variable and participant as a random independent variable, chi square=5.14, p=0.023; Fig. 1D). This effect also arose when we entered working memory capacity (a proxy for baseline dopamine synthesis capacity) as a regressor of no interest into the model (chi square=5.01, p=0.025). Please note that amisulpride did not cause participants to become risk seeking, as the proportion (50.2%) of high variance choices in the treatment group was not significantly different from 50% (one-sample, one-tailed t-test, t_{44}=0.49, p=0.62), suggesting that under amisulpride participants were risk-neutral.

Participants under amisulpride were also more likely to choose the higher expected value option than participants under placebo (mixed effects logistic regression, chi square=6.89, p=0.008; with working memory capacity as a regressor of no interest: chi square=6.46 and p=0.011; Fig.

1E). Although risk and expected value are necessarily correlated in our task (to avoid decisions where one option strictly dominates the other), we ran a multiple mixed effects logistic regression to assess if amisulpride affected high expected value choices and higher risk choices to different degrees. There was no significant difference in the regression weights between expected value and risk (one-sample t-test, t_{147}=-1.11; p=0.85), suggesting that reduced risk aversion under amisulpride arose from similar effects on expected value and risk processing.

To determine if reduced risk aversion in the amisulpride group could be explained by increased choice randomness under amisulpride, we ran a test assessing the number of consecutive choices above or below the mean of the choice vector (implemented using Matlab's 'runstest' function). This showed that the choice profile in both the amisulpride and placebo groups was not random (Z=-1.09; p=0.28). Additionally, participants under amisulpride were less random in their choice of the higher expected value option than participants under placebo (Fig. 1E). Moreover, model-based analyses showed that if anything, amisulpride was associated with less variation in behavior, both in probability distortion and loss aversion (see below). Finally, response times did not differ between the amisulpride and placebo groups (two-sample t-test, t_{91}=-0.44; p=0.66), providing no evidence that the amisulpride group made choices less carefully than the placebo group.

A decrease in risky choices under amisulpride could arise from increased linearity in the curvature of the utility function, a reduction in loss aversion, changes in the probability weighting function, or a combination. To investigate these possible channels of amisulpride action, we recovered the σ, λ, and α parameter values for each participant by fitting a prospect theory model to the choice data using hierarchical Bayes. Using the average parameter values from the fitting, we plotted the recovered utility function across arbitrary amounts. Visual

inspection of this average utility function (Fig. 2A) showed a more linear function (and decreased probability distortion; see below and Fig. 3) for the amisulpride group. This impression was confirmed by directly comparing the best fitting parameters, with the amisulpride group showing significantly less curvature (i.e. the σ parameter was closer to 1) than the placebo group (amisulpride=0.741; placebo=0.548; t_{91}=-3.82 p=0.0001; two-sample t-test; p=0.0003 when controlling for working memory; p=0.0002 when controlling for weight; Fig. 2B). Thus, participants under amisulpride exhibited significantly decreased concavity in their utility functions.

To further illustrate these findings, we next used the individual utility curvature parameters to transform objective outcome magnitudes into subjective values. Using the best fitting utility curvature parameter (σ) for each participant, we inferred the subjective value of objective reward magnitudes with the power utility function specified according to prospect theory (i.e., objective monetary magnitude in Swiss francs raised to the power of σ for each participant). A two-way ANOVA with objective monetary magnitude (CHF 5, 10, 30, 40 & 100) and treatment (amisulpride/placebo) as factors revealed a significant interaction effect of treatment and monetary magnitude ($F_{4,92}$=4.07, p=0.003), with participants under amisulpride showing increased sensitivity to outcome magnitudes as these magnitudes increased (Fig. 2C). Thus, behavioral choices under amisulpride were in agreement with the notion that participants assessed gain and loss magnitudes in the risky options in a more linear and objective fashion.

Next, we assessed whether the more linear value function under amisulpride (Fig. 2C) translated into increased sensitivity to expected value. To test this possibility, we calculated the expected values (probability x magnitude) of all options presented to each participant. Then we performed a mixed effects logistic regression to assess the influence of expected value on the probability of

participants selecting the higher expected value option. If amisulpride increased expected value sensitivity, one would expect to see significantly larger regression weights for high expected values in the amisulpride group. Indeed, a two-way ANOVA revealed a significant interaction effect of high (larger than median rank of 100 Swiss francs) versus low (smaller than median) expected values with placebo versus amisulpride treatment ($F_{2,10}$=4.99; p=0.046), indicating higher expected values had a significantly different impact on choices for the two groups (Fig. 2D). Fisher r-to-z transformation confirmed that the increasing value sensitivity was significantly more tightly correlated to increasing expected value in the amisulpride group compared to the placebo group (Z=2.1, p=0.02). These data suggest that the value processing system under amisulpride indeed becomes more sensitive to increases in expected value.

Because expected value incorporates both magnitude and probability information, one possibility is that amisulpride affects not only value curvature but also probability distortion. Indeed, visual inspection of the probability weighting function for the two groups suggests that amisulpride reduced probability distortion (Fig. 3A). To test this possibility quantitatively, we directly compared the probability distortion parameters for the two groups. Compared to placebo, probability distortion was significantly lower under amisulpride (amisulpride=1.059; placebo=0.804; t_{91}=-4.63 p=0.0001 two-sample t-test; p=0.0001 controlling for working memory capacity; p=0.0001 controlling for weight), resulting in a more linear mapping of objective probabilities and less heterogeneity in probability distortions (Fig. 3B & E). Specifically, in the amisulpride group α values ranged from 0.56 to 1.52, whereas in the placebo group they ranged from 0.26 to 1.56 (Fig. 3D). A Bartlett's test for the equality of variances in the revealed functions showed a significantly smaller spread in probability distortion in the amisulpride group (Bartlett's test statistic=7.79; p=0.005). This more linear mapping of objective probabilities

under D2/D3 receptor blockade could result in less risk aversion for lotteries with typically large probabilities that were underweighted by the placebo group.

To determine whether reduced utility curvature or probability distortion was the primary driver of reduced risk aversion under amisulpride, we regressed participants' choice frequency of high risk and high expected value options against treatment*parameter interactions simultaneously (multiple linear regression). For high risk choices, both utility curvature (β=0.15; p=0.0001) and probability distortion (β=0.06; p=0.02) parameters impacted choice, but compared to probability distortion (R^2=0.19), utility curvature explained significantly more variance (R^2=0.28) in the frequency of riskier choices (linear hypothesis test on coefficients, F=21.58; p=0.0001). A similar pattern arose for high expected value choices (utility curvature β=0.22; p=0.0001; probability distortion β=0.08; p=0.02), with utility curvature explaining significantly more variance (R^2=0.42 compared to R^2=0.25; linear hypothesis test on coefficients, F=17.49 p=0.0001). Thus, amisulpride effects on both parameters significantly impacted choices in our data, but within the range of decisions used in our task, the effect on the utility curvature parameter appeared to have a significantly higher impact on driving decreased risk aversion.

The two groups did not differ significantly in the recovered loss aversion parameters (amisulpride=1.412; placebo=1.409; t_{91}=-0.35, p=0.73; two-sample t-test; Fig. 3C). A two-way ANOVA with parameter values (α, σ, and λ), and group treatment as factors confirmed that there was no significant effect of the drug on participants' loss aversion parameters (p=0.99) in our task, suggesting that dopamine may be more strongly involved in coding the subjective processing of probability and gain magnitude rather than loss aversion. It may be worth noting that also this analysis showed significantly less variance in the parameter estimates for the amisulpride group than the placebo group (Bartlett's test statistic=17.62, p=0.001; Fig. 3C),

again indicating that amisulpride did not simply increase randomness in choice behavior. Overall, utility curvature and probability distortion were significantly correlated (R^2=0.27; p<0.001). There was no significant correlation between utility curvature and loss aversion (R^2=0.03; p=0.09) or probability distortion and loss aversion (R^2=0.03; p=0.11). For the amisulpride group, there was no correlation in parameter values and behavioral measures with weight (all p-values >0.1).

Finally, we computed both the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for each model fit, penalizing more complex models by correcting for the number of free parameters. We then used Bayesian model comparison to determine which model (prospect theory, expected utility or expected value) best explained the observed choices in both groups. Focusing on AIC in the placebo group, prospect theory fitted the observed choices significantly better than expected utility and expected value models (Fig. 4A; exceedance probability=1.0; p=0.001; 38/48 participants classified as prospect theory types). In striking contrast, in the amisulpride group, expected utility theory fitted behavior significantly better than prospect theory (Fig. 4B; exceedance probability=1.0; p=0.03; 28/45 participants classified as expected utility types). Comparison of BIC also confirmed this result (Supplementary Fig. S4). Thus, the expected utility model best explained choice behavior when D2-receptor action was blocked.

Discussion

Our results indicate a key role for the dopaminergic system in the processing of subjective values during risky decision making. Specifically, D2/D3 receptor antagonism reduced risk aversion. Computational modeling revealed that this effect arose from two channels: an increase in the linearity of the utility curvature, reflected in higher sensitivity for larger reward magnitudes, and a decrease in probability distortion. By extension, the expected utility model explained choice behavior best under amisulpride whereas prospect theory had the highest explanatory power under placebo.

By concurrently and systematically estimating all three parameters governing risky decision making according to prospect theory we assessed the effects of D2/D3 receptor blockade on each parameter separately, which provides a clear advance to the literature (St Onge & Floresco, 2009; Kandasamy *et al* 2014; Sokol-Hessner *et al* 2015). The linearized utility curvature and probability distortion functions under amisulpride are exactly what would be expected if dopaminergic projections and dopaminoceptive neurons of the nigrostriatal or mesolimbic systems are involved in coding the subjective value of risky choice options. Indeed, the two

parameters co-determine subjective value and affect choice, both in humans (Kahneman & Tversky, 1979) and other animals, such as non-human primates (Stauffer *et al* 2015).

Previous studies have clearly demonstrated that dopaminergic manipulation has an effect on risk taking. For example, L-DOPA (which, after conversion to dopamine, stimulates both D1 and D2 receptors concurrently) has been shown to increase choices for riskier gambles involving small-stake gains (but not those involving small-stake losses) and increase baseline gambling propensity (Rutledge *et al* 2015; Rigoli *et al* 2016) in a value independent fashion. In line with these findings, our data show that dopamine is important for risk taking and that it is less involved for loss than for gain processing during risky choices. In addition, the present findings reveal that receptor-specific dopamine manipulations can affect risky choice and that the effects arise through effects on utility and probability distortion. Moreover, our data show that the effect of amisulpride depends on value and is particularly pronounced at high expected values. This finding is in line with a multiplicative rather than an additive effect of the drug on value processing (Zhang *et al* 2009) and suggests that it may be important to use a large range of possible outcomes. The finding that dopamine D2/D3 receptor blockade also reduces discounting of larger later rewards (Weber *et al* 2016) suggests that the mechanism of increased sensitivity to larger gain magnitudes generalizes to other forms of value-based decision making.

A major target for dopamine neurons is the striatum and other parts of the basal ganglia that regulate the selection versus inhibition of actions through a direct pathway onto internal globus pallidus and substantia nigra pars reticulata versus an indirect pathway on these structures via the external globus pallidus. The direct, D1-mediated (go) pathway facilitates the learning of actions to approach rewards, whereas the indirect D2-mediated (no-go) pathway inhibits behavioral responses and facilitates learning from subjectively less valued outcomes (Cox *et al* 2015;

Kravitz *et al* 2012). Dopamine has opposing actions in the two pathways. At D2-neurons, dopamine facilitates inhibition of the indirect pathway by impeding up-state transitions, diminishing up-state spiking and promoting long-term depression at excitatory glutamatergic synapses (Surmeier *et al* 2014). Accordingly, postsynaptic D2 antagonism should boost the indirect pathway, resulting in increased competition between the direct and the indirect pathway and possibly other regions of the brain (Lee *et al* 2016). In this regard, it is worth noting that dopamine actions on D4 receptors in the cingulate cortex (Cocker *et al* 2016) and D2 receptors in the insular cortex (Ishii *et al* 2015) affect risk taking. As the indirect pathway is thought to be associated with no-go responses, one speculative notion may be that D2 antagonism renders actions and alternatives that would normally not be chosen more viable and subjectively valuable. This notion is consistent with our finding that under amisulpride more risk-neutral choices were facilitated by both high magnitude and high probability choices, resulting in the selection of actions which would not normally be chosen. The notion is also consistent with our previous findings of amisulpride reducing reward impulsivity (Weber *et al* 2016) and of amisulpride enhancing vs. reducing generosity in men vs. women (Soutschek *et al* in press).

More specifically, blocking D2-neurons may prevent the value-reducing action of D2-neuron stimulation by dopamine, providing a mechanistic explanation why people became more risk seeking in our study. This interpretation concurs with the finding that stimulating D2-neurons in the nucleus accumbens during the decision phase decreases risky choice of risk seeking rats in the stimulated trial (Zalocusky *et al* 2016). Thus, D2-neuron stimulation by dopamine may reduce the value of risky choice options and our data suggest that this effect could be prevented by amisulpride. Related effects have also been demonstrated in learning situations, with the D2 antagonists such as haloperidol facilitating learning from rewards and D2 agonists such as

cabergoline reducing the ability to learn from rewards (Frank *et al* 2004; Frank *et al* 2007). However, to fully test the possibility that D2 blockade is specifically involved in utility curvature and probability distortion and exclude a less specific effect of reduced dopamine action, it would be necessary to perform a similar experiment with D1-receptor specific compounds.

Our results also lend weight to the role of D1 and D2 receptors in the regulation of value encoding proposed by a recent model of uncertain reward learning in the basal ganglia that postulates reward magnitudes are encoded in the difference between the synaptic weights of D1- and D2-neurons whereas reward uncertainty is coded in the sum (Mikhael & Bogacz, 2016). Blocking the D2-mediated dopaminergic pathway could increase the difference between D1 and D2 synaptic weights, causing a concomitant increase in magnitude sensitivity as shown in our data. The sum of synaptic activity should also decrease, thus decreasing uncertainty coding and causing a decrease in risk aversion relative to the placebo group, offering an alternative potential mechanism for the reduction of risk aversion reported here.

While amisulpride reduced risk aversion, it did not cause participants to become risk seeking, evidenced by the increased linearity of the utility and probability weighting functions. It remains unclear if higher doses of D2 antagonists would cause the shape of the utility function to become convex (and thus induce risk seeking by further increasing sensitivity to increasing monetary magnitudes). The literature on medication-induced pathological gambling in Parkinson' disease (Molina *et al* 2000; Driver-Dunckley *et al* 2003) may suggest that this possibility is worthy of further investigation.

Amisulpride not only increased sensitivity to reward magnitude but also reduced probability distortion. This effect is in line with the expected utility model of risky decision making (Bernoulli, 1954; von Neumann & Morgenstern, 2007) and was reflected in the increased fit of

this model compared to prospect theory under amisulpride. By contrast, under placebo, prospect theory provided a better model fit than expected utility. Together, these findings suggest that deviations from expected utility-like decision making are driven by D2 actions.

In contrast to the effects on magnitudes and probabilities, our data showed that loss aversion remained unaffected by an acute dose of amisulpride. This finding is compatible with the notion that dopamine preferentially processes the value of rewards rather than punishments (Fiorillo, 2013). However, it has been shown that tonic stimulation of D2/D3 receptors can change the subjective value of losses (Campbell-Meiklejohn *et al* 2011) and reduce negative reward prediction error encoding (van Eimeren *et al* 2009; but see Pessiglione *et al* 2006). It is conceivable that using higher doses of amisulpride would have affected loss aversion in our task. However, it is worth keeping in mind that the subjective definition of a loss is highly dependent on the reference point which may vary across experimental designs and participants (Walasek & Stewart, 2015).

Amisulpride is relatively selective for D2/D3 receptors but acts also on serotonergic 5-HT7-receptors (Abbas *et al* 2009). While it has been related to memory formation and sleep (Gasbarri & Pompili, 2014), the role of the 5-HT-7 receptor for value-based decisions is largely unknown. However, given that serotonin (5-HT) has been associated with punishment processing and response inhibition (Cools *et al* 2008) and with counteracting dopamine (Daw *et al* 2002), it seems unlikely that the present effects are due to 5-HT7 actions of amisulpride. Another limitation to the interpretation of our results is that the effects of dopaminergic drugs on cognitive functions are sensitive to baseline dopamine synthesis capacity, which we measured only indirectly in the current study through digit span (Cools *et al* 2009). The fact that all our effects were robust to inclusion of digit span data raises the question whether baseline synthesis

capacity plays less of a role for risky decision making than for more cognitive tasks. Although our groups were matched for BMI, another potential limitation is that we did not adjust mg/kg dosage per participant in the amisulpride group or take blood plasma readings to assess drug uptake at the time of the task. Our previous research showed little relation between blood plasma levels of amisulpride and value-based behavior (Weber *et al* 2016). Moreover, we did not find strong correlations between weight and behavioral effects. However, to fully assess the consequences of D2 antagonism on value processing it would be necessary to investigate dose response curves in future studies. Finally, the temporal specificity of D2 antagonism is difficult to judge using our study design, and the question whether amisulpride affects decisions at the time point of valuation or choice remains to be determined.

In conclusion, this research sheds light on the specific role of dopaminergic activity in encoding subjective reward magnitude and probabilities during risky choice. Blockade of D2/D3 receptors straightened both value and probability weighting functions, resulting in more risk neutrality. Moreover, our findings specify the mechanisms that may underlie behavioral side-effects of dopaminergic medicines (either antagonistic or agonistic) used in the treatment of psychiatric and neurological disorders and demonstrate the differential roles of the D1- and D2-mediated pathways in the processing of value in risky decision making.

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Figure Legends

Figure 1. Potential effects of amisulpride on utility function, illustration of example trial and observed effects of amisulpride on choice behavior. **A, B**. Prospect theory proposes an asymmetrical, nonlinear and concave mapping of subjective value on increasing monetary gains and losses that results in different risk attitudes of individuals. **A,** potential effect of D2/D3-blockade on reducing the curvature of the value function (red dashed line; prospect theory utility curvature parameter σ=0.7) compared with placebo (blue; σ=0.5). **B**, potential effect of D2/D3-blockade on reducing loss aversion (red dashed line; prospect theory loss aversion parameter λ=1.5) compared with placebo (blue line; λ=2). Note that solely manipulating the loss aversion parameter does not affect value sensitivity in the gain domain. **C**. Example trial. After a fixed intertrial interval of 2 seconds, participants made a self-paced choice (20 in total) between risky options that varied in gain and loss magnitudes and probabilities and which were presented on the left and right sides of the screen. **D**. Participants in the amisulpride group chose the riskier (higher variance) option significantly more often than participants in the placebo group, indicating decreased risk aversion. **E**. Amisulpride resulted in more frequent choices of the high expected value option, consistent with increased value sensitivity.

Figure 2. Observed effects of amisulpride on subjective value function from prospect theory. **A**. Fitting a prospect theory model to participants' choices revealed a significantly more linear value function for the amisulpride (red) relative to the placebo group (blue). **B**. These findings were supported by utility curvature (σ) parameters being significantly closer to 1, i.e. linearity (gray dashed line) in the amisulpride group. Boxplots show the mean (+), and median (-), which coincided; boxes represent 25th and 75th percentiles and whiskers the 9th and the 91st percentile.

C. Recovered value functions for different reward magnitudes revealed a steeper and more linear function for the amisulpride group (red), indicating lower risk aversion when compared to the placebo group (blue) **D**. Since both utility curvature and probability weighting (Fig. 3) functions were more linear under amisulpride, sensitivity to increases in the expected value of the option should also be increased. This was confirmed by a logistic regression of choices of the higher expected value option against the expected value of the option, which allowed us to estimate regression weights as a proxy for the expected value sensitivity in the two groups. Participants rarely encountered extremely high option magnitudes as they were associated with high risk. Accordingly, we could not plot an error bar for the amisulpride group at CHF 1000. Error bars represent the standard error of the mean.

Figure 3. Effects of amisulpride on probability distortion and loss aversion. **A**. Average probability weighting functions were less distorted in the amisulpride group (red) than in the placebo group (blue). **B**. Accordingly, probability distortion (α) parameters were significantly closer to 1 for the amisulpride compared to the placebo group. **C**. Groups did not differ significantly in mean loss aversion (λ) parameters. In B and C, boxplots show the mean (+) and median (-); boxes represent 25th and 75th percentiles and whiskers the 9th and the 91st percentile, with the gray dashed line representing 1 (i.e. linearity). **D**. To better visualize individual probability weighting functions we randomly selected 15 participants in the placebo group (whole group shown in inset). Similar to the full group, probability distortions were more pronounced and varied more widely in these participants. **E**. In contrast, the amisulpride group showed more homogeneous and reduced probability distortions, both in randomly selected 15 participants and in the full group (inset).

Figure 4. Estimated model frequencies from Bayesian model comparison. **A**. For the placebo group, prospect theory (PT) best explained choices in 38/48 participants, and was the best fitting model overall (highest exceedance probability) in comparison to expected utility (EU) or expected value (EV) models. **B**. In contrast, the expected utility model best explained choices in the amisulpride group, with 28/45 participants being classified as EU-types. Dashed lines in both panels denote the probability that all models perform equally well at best fitting participants.